Alopecia areata induced by the booster shot of Sinovac COVID-19 vaccination: a case report

Several COVID-19 vaccines have been developed to date in an effort to slow the spread of SARS-CoV-2 infections and to reduce disease-related morbidity and mortality. These COVID-19 vaccines have the potential to induce immune-mediated adverse side effects, particularly in young women diagnosed with pre-existing autoinflammatory or autoimmune conditions [1]. Here, we report a 20-year-old woman who developed alopecia areata (AA) two weeks following a booster shot of the Sinovac COVID-19 vaccine, which is an inactivated SARS-CoV-2-specific vaccine produced in China.

In April 2022, a 20-year-old woman presented to our outpatient clinic with multiple hairless patches throughout her scalp. She did not report any personal or family history of AA or other autoimmune diseases, and indicated that this progressive hair loss had occurred rapidly over the two-week interval since she received a Sinovac COVID-19 vaccine booster shot. She had not experienced any apparent hair loss after receiving either of the two previous doses of this vaccine, nor did she report a history of symptomatic COVID-19 infection. Two days prior to her most recent booster shot, a COVID-19 naso-oropharyngeal swab test proved negative. Physical examination revealed multiple patches of alopecia on the scalp without any evidence of scarring or inflammatory erythema. The Severity of Alopecia Tool (SALT) score was 30 (*figure 1A-C*). No other cutaneous or systemic abnormalities were found upon general examination. The pull test was diffusely positive. Dermoscopy (FotoFinder bodystudio ATBM) examination revealed broken hairs, black dots, and some exclamation-mark hairs, consistent with active AA (*figure 1D*). No evidence of fungal infection was observed, and all laboratory tests, including those for thyroid function, anti-thyroid antibodies, antinuclear antibodies, and IgE levels, were within normal limits. The patient was prescribed a combination of topical and oral steroids, and is currently undergoing clinical follow-up.

AA is an autoimmune disease that arises in genetically susceptible individuals and is characterized by non-scaring hair loss. While the specific causes of AA remain poorly understood, hair bulb inflammation and the disruption of the normally immune-privileged status of hair follicles are thought to contribute [2]. Several environmental triggers have been proposed, including dietary factors, hormonal changes, psychological stress, viral infection, and even vaccines [3].

To the best of our knowledge, only a few cases of AA occurring following COVID-19 vaccination have been reported in the literature [3-8]. We describe here the first known case of AA triggered by a booster shot of the inactivated Sinovac COVID-19 vaccine developed in China, although we cannot exclude the possibility that this patient had previously unnoticed AA following her initial two doses of this vaccine.

The adverse immune-related side effects associated with COVID-19 vaccination may be governed by several different processes, including molecular mimicry-mediated production of pathological autoantibodies [9]. The adjuvants used in these vaccines to provoke a more robust immune response can also induce non-specific inflammation or autoimmunity, and may cause alopecia in some individuals [10]. The timing of AA onset in this case is consistent with the hypothesis that COVID-19 vaccination triggered the development of an autoimmune response in a susceptible patient. The inactivated Sinovac vaccine is composed of viral particles that are unable to infect cells or replicate, but maintain the active viral structures necessary to induce an appropriate immune response. In this patient, the two initial doses of this vaccine may have been sufficient to break immune tolerance such that their hair bulbs were subject to a vigorous autoimmune attack upon booster shot-mediated sensitization, ultimately culminating in overt AA. We posit that these underlying processes may be at least partially associated with COVID-19 vaccine-induced upregulation of cytokines, including interleukin-6 (IL-6) and interferon-γ (IFN-γ). IFN-γ plays a central role in the pathogenesis of AA by driving an increased expression of major histocompatibility complex class I molecules that may potentiate the loss of immune privilege normally experienced by human hair follicles. IL-6 can also suppress follicular keratinocyte and hair follicle stem cell proliferation, thereby inhibiting the telogen-to-anagen transition [5]. However, additional studies are necessary to fully understand the risk of autoimmunity in susceptible individuals following COVID-19 vaccination.

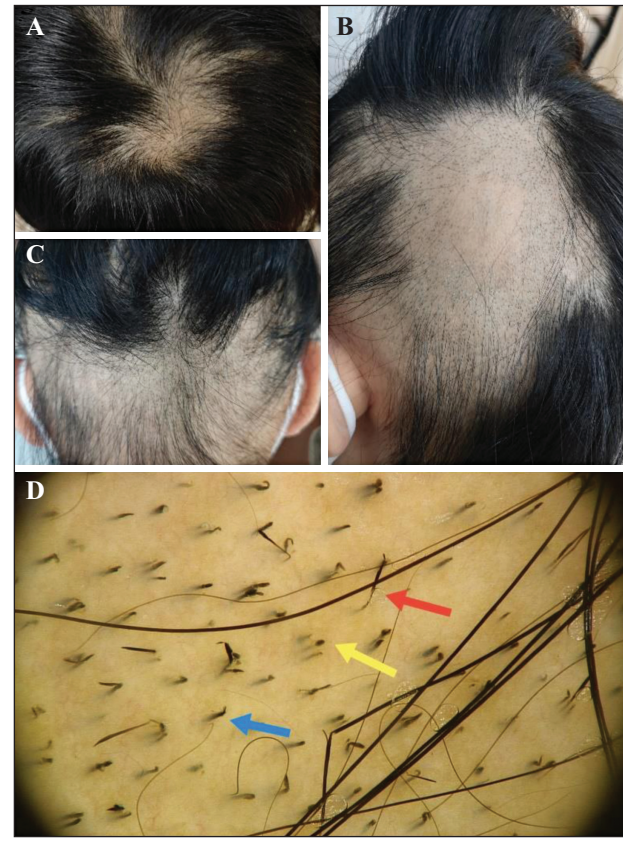

Figure 1. **A**) A single bald patch localized at the vertex. **B**) Diffuse alopecia at the occipital region. **C**) Large hairless patch localized at the left temporal area. **D**) Dermoscopic image at the left temporal area showing black dots (yellow arrow), broken hairs (blue arrow) and some exclamation mark hairs (red arrow).

Acknowledgments and disclosures. *Acknowledgments: none. Funding: this study was supported by Hangzhou medical key discipline construction project (No. [2021]21-3). Conflicts of interest: none. Statement of written informed consent: written informed consent was obtained from the patient for the use of images and publication of her case details.*

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doi:10.1684/ejd.2022.4363

Successful rechallenge for severe lichenoid drug reaction to pembrolizumab presenting as "toxic epidermal necrolysis-like"

Immune checkpoint inhibitors (ICIs) lead to cytotoxic T-cell activation and subsequent elimination of cancer cells, often resulting in immune-related adverse events (irAEs). Anti-programmed death 1 (PD1) antibodies cause cutaneous irAEs in up to 40% of patients [1]; most of them are mild and do no impact treatment continuation. A few cases of severe lichenoid-like eruptions, named "toxic epidermal necrolysis (TEN)-like" have been described [2]. We report the first case of anti-PD1 rechallenge after a TEN-like eruption.

A 55-year-old man had Stage IV melanoma, with *BRAF* V600E mutation, in progression after encorafenib plus binimetinib. Pembrolizumab (2 mg/kg/3 weeks) was started while continuing targeted therapy during the first three weeks. Seventeen days after pembrolizumab infusion, an extensive maculopapular rash appeared. Blisters and epidermal detachment with Nikolsky sign on the trunk and limbs were present, associated with oral erosions, cheilitis and conjunctivitis, however, the general status was unaltered and no fever was present (*figure 1A*). Laboratory work-up showed increased CRP (55 mg/L), no eosinophilia, normal renal and hepatic function, and no virus reactivation. We suspected an anti-PD1-induced Grade 4 skin toxicity [1] and stopped the infusions. Histological examination showed a pustular and lichenoid neutrophilic and lymphocytic interface dermatitis and a moderate perivascular lymphocytic and neutrophilic infiltrate with extravasation of red blood cells without vasculitis (*figure 1B*). A second biopsy taken at another body site showed a subepidermal blister filled with neutrophils and lymphocytes with a partially necrotic epidermal roof, scattered intraepidermal necrotic keratinocytes, and preserved stratum corneum (*figure 1C*). Direct immunofluorescence was negative. Prednisone at 1 mg/kg/d was started, combined with local clobetasol. One week later, re-epithelialization was nearly complete and prednisone was stopped. Rash recurrence was observed one month after, with diffuse skin erythema, blisters, and oral lichenoid-like lesions, again regressive with corticosteroids.

Considering the clinicopathological presentation and outcome, *i.e*. slight mucosal involvement, good general condition, lichenoid oral recurrence, predominance of interface dermatitis, and rapid favourable evolution with corticosteroids, we classified this skin toxicity as a severe "TEN-like" form of bullous lichenoid drug eruption [3].

Based on possible cerebral metastatic progression, recent resistance to targeted therapies, and in the absence of a therapeutic alternative, we decided to rechallenge with immunotherapy by switching to nivolumab (3 mg/kg/2 weeks), combined with systemic corticosteroids (1 mg/kg/d). Although the anti-PD1 antibody structure is very similar [4], we decided to switch based on clinical studies reporting more severe irEAs with pembrolizumab than with nivolumab [5]. No skin recurrence occurred after four months of nivolumab treatment, but the patient died from melanoma.

Some life-threatening cutaneous irAEs have been described in patients treated with ICIs [2], manifesting with severe erosive or bullous lesions. The diagnosis of TEN may be challenged and ultimately most of these cases can be diagnosed as severe bullous lichenoid eruptions [3].

Classic TEN begins 4-28 days after drug exposure with confluent erythema, and progresses rapidly to epidermal detachment. Two or more mucous membranes are involved in 80% of cases, in association with general physical deterioration and fever. Histologically, full-thickness epidermal necrosis and detachment is observed [6]. Conversely, in TEN-like severe lichenoid eruption, the interval seems longer (an average of three weeks for nivolumab and 11 weeks for pembrolizumab [2]) and the general condition is preserved. Mucosal involvement is milder, involving less than two sites, with no severe evolution. The lichenoid clinical aspect is an additional argument, sometimes visible only during follow-up (as in this case). A prominent lymphocytic infiltrate with few necrotic keratinocytes is suggestive of lichenoid eruption [3]. Auto-immune blistering diseases should be ruled out with direct immunofluorescence.